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   Central Research Laboratories Limited
   Dawley Road
   HAYES
   Middlesex UB3 1HH
   UK

   Patents ADP number *(if you know it)*

   6097943001

   If the applicant is a corporate body, give the country/state of its incorporation

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4. Title of the invention

   Apparatus For, And Method Of, Controlling The Rate Of Flow Of Fluid Along A Pathway

5. Name of your agent *(if you have one)*

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APPARATUS FOR, AND METHOD OF, CONTROLLING THE RATE OF FLOW OF FLUID ALONG A PATHWAY

This invention relates to an apparatus for and method of controlling the rate of flow of a fluid along a pathway. More particularly, but not exclusively, the invention controls the rate of flow of fluid along a pathway in a wet chemistry analysis system.

A common feature of all "wet chemistry" analysis or assay systems is that analyte, together with one or more reagents, usually passes through a series of processes or procedures. These include: mixing, reacting, incubating, filtering, decanting, metering and dividing. In short, some form of fluid handling is a common and important feature of most assay systems.

International Patent Application WO-A1-9419484 (Biocircuits Corporation) describes a disposable device for use in diagnostic assays and comprises a number of chambers and interconnecting pathways. Capillary valves are used to enhance control over fluid flow in the device. One type of capillary valve comprises a fluid flow capillary channel and a control capillary channel which intersect each other at right angles. The intersection disrupts fluid flow in the flow capillary channel when the control capillary is empty, but does not impede flow through the flow capillary channel when it is full. Thus, fluid flow through the device can be controlled by either filling or emptying the control capillary with liquid.

A similar disposable device is described in International Patent Application WO-A1-9727324 (David Sarnoff Research Center). This device uses valves and pumps for controlling the flow of fluid. The valves used may be of the plunger type such that the valve has a piston and plunger rod. The diameter of the plunger rods is typically of the order of 60μm and the piston diameter is typically of the order of 200μm.

In conventional analysis techniques, fluid handling relies on precisely engineered fluid controllers such as valves, taps and fluid delivery systems. These fluid controllers are expensive and difficult to manufacture. They are therefore not appropriate for inclusion in disposable units due to their number and cost.

An aim of the present invention is to overcome the aforementioned problems by providing a means for accurately controlling the flow of fluid along a pathway.

According to the present invention there is provided an apparatus for controlling the rate of fluid flow along a pathway of an envelope, the envelope comprising at least one chamber in fluid connection with the pathway, and a thermally activated material disposed within the envelope, whereby in use, a change of state of the thermally activated material causes a change of the rate of fluid flow along the pathway.

More particularly, fluid flow along a pathway of the apparatus is controlled by way of valves, or clamps, which may be opened and/or closed upon the application of heat and/or pressure. The valves and clamps may comprise a thermally activated material.

When heat is applied to the pathway containing the thermally activated material, the material changes its position, size, state or function. This causes a rate of change in the fluid flow in the pathway. Thus a pathway which is initially obstructed becomes unobstructed, and vice versa.

Hereinafter, a gate that opens a pathway to the flow of fluid on application of heat is known as a heat openable gate. A gate that closes a pathway to the flow of fluid on application of heat is known as a heat closable gate.

Means may be provided for the supply and/or removal of heat from the apparatus in order to melt and/or the wax valves and clamps. Heater elements may be printed onto the apparatus, or be supported by a separate heating tool, which may be used to apply heat to local areas of the apparatus. Alternatively, heat may be applied to or removed from larger regions of the apparatus, or to a device which includes the apparatus. For example, by dipping into a water bath, heating with an external heater, or by a Peltier.

Preferably the thermally activated material is wax, or any material such as polypropylene polystyrene, a wax/polymer mix, a metal such as Indium, or any other suitable low melting

point material that changes its state on application of heat, and on cooling. The terms thermally activated material and wax are hereinafter used interchangeably.

Alternatively at least one recess is located substantially adjacent the pathway which receives thermally activated material. Most preferably the recess has a vent leading thereto or therefrom. Thermally activated material may be situated in said at least one recess substantially adjacent the pathway.

One example of a heat openable gate has thermally activated material situated in the pathway, so as to enable the material in its melted state to flow into at least one recess substantially adjacent the pathway. Air (or other gas) is displaced from the recess by the material and exits through a vent. A type of heat closable gate has thermally activated material situated in at least one recess substantially adjacent the pathway. As the material in its melted state flows from the recess into the pathway, it is replaced by air (or other gas) via the vent.

Alternatively, (or in addition to the material being situated in at least one recess), the material may be situated in the fluid pathway such that the pathway is either substantially or partially obstructed. If the thermally activated material is substantially obstructing the pathway, then the pathway may be opened to the flow of fluid by applying heat to the material. This is a form of heat openable gate. However, if the material is situated so as not to, or only partially, obstruct the flow of fluid, on application of heat the material melts and flows so as substantially obstruct the pathway. This is a form of heat closable gate.

In a further alternative embodiment, thermally activated material may be arranged to contact at least two points on inner surfaces of the envelope, forming a clamp. Clamps may be situated in chambers. Upon application of heat to a clamp, the clamp melts, and surfaces of the chambers are separated. Thus a pressure differential is provided to drive fluid along pathways and into or from chambers.

The envelope may contain at least one region that repels or attracts the thermally activated material. A region having such a property is hereinafter referred to as being hydrophobic.

Thus the flow of material is guided along a predetermined path and discouraged from contacting other regions of the envelope.

Preferably at least one surface contained within the envelope is resiliently deformable. This is advantageous because it means that if the surfaces are constructed from sufficiently pliable materials, pressure may be applied to a surface, and the surfaces will return to their original state.

Pressure may also be applied to a pathway. The pathway may contain a volume of material, so that upon application of pressure, a rate of change of fluid flow in the pathway occurs. The material may be thermally activated. Thus for a heat closable pathway, a tool may be used to seal the pathway by connecting the upper and lower surfaces with the thermally activated material. Thermally activated material may not be required if the upper and lower surfaces of the pathway may be directly connected to one another. For a heat openable pathway, a tool may make a channel in the wax contained in the pathway. When this occurs the resiliently deformable material of the pathway returns to a previous state. Pathways opened in this way may be resealed by heating and subsequent cooling of the wax.

Preferably the volumes of thermally activated material may be accessed independently and sequentially to precisely control the path of fluid flow in the apparatus.

Valves and clamps may be single use structures, or may be reusable.

The invention may be incorporated into a chemical assay device. The assay device is usually rectangular, but other shapes are equally viable, such as discs or hexagons. Depths of fluid pathways and chambers may be sufficiently narrow to allow filling by capillary action (say 0.02 to 0.2 mm). Pathways may be wider (of the order of a millimeter) where the fluid flow is to be propelled by gravity, a pressure impulse, centrifugal force, or an inertial force. The aforementioned dimensions are consistent with processing fluid samples in the range of approximately 30 to 50 microlitres, and are given by way of example only.

The body of the assay device is preferably formed from a polymer or from a combination of materials including glass, ceramics, or metal. Construction may involve injection moulded components, and/or the joining together of a number of laminae. Channels and chambers in the assay device may be formed in a plane defined between upper and lower planar sheets. Channels and chambers may be formed by printing, etching, ablation or cutting of the substrate, or moulding of a substrate, or a combination of these. More complex structures may be realised by building up laminae and providing vias for the flow of fluids between adjacent levels.

Bonding of upper and lower portions of the device is critical for its operation. Bonding can be achieved by means of screen printed adhesives containing for example spacer balls, by cut adhesive gasket materials, by heating sealing, by uv curing, by mechanical fixing, by ultrasonic bonding, or by using a porous-gasket technique, for example as described in US-A-4,865,716.

The assay device may include one or more of the aforementioned gates, valves or clamps.

Wax gates and clamps may also be printed, using molten wax or wax dissolved in a solvent, by injection of molten wax into the device using feeder tubes, or by placing individual wax elements within the apparatus using pick and place equipment.

Provision may be made for fluid overflow lines, for collection of waste, and for opening and sealing of the device at stages from start of use until disposal.

Embodiments of the invention will now be described by way of examples, and with reference to the accompanying Figures in which:-

Figure 1 is a schematic plan view of a chemical assay device incorporating the invention;

Figure 2a is a plan view of part of a device and shows a pathway having an initially open wax gate, where wax is situated in recesses adjacent the pathway;
Figure 2b shows a plan view of the pathway of Figure 2a, where the wax gate has been closed upon the application of heat to the gate;

Figure 3a shows a plan view of a pathway having an initially open wax gate, where a volume of wax is situated in the pathway;
Figure 3b shows a plan view of the pathway of Figure 3a, where the wax gate has been closed upon the application of heat to the gate;

Figure 4a shows a plan view a pathway having an initially open wax gate, where a volume of wax is situated in the pathway;
Figure 4b shows a cross-section of the pathway of Figure 4a;
Figure 4c shows a cross-section of the pathway of Figure 4a, the pathway having been closed on application of heat and pressure;

Figure 5a shows a plan view of a pathway having an initially closed wax gate, where wax is situated in the pathway, and recesses adjacent the pathway;
Figure 5b shows a plan view of the pathway of Figure 5a, where the wax gate has been opened upon the application of heat to the gate, wax having flowed into the recesses adjacent the pathway;

Figure 6a shows a plan view of a pathway having an initially closed wax gate, where a volume of wax is situated in the pathway;
Figure 6b shows a plan view of the pathway of Figure 6a, where the wax gate has been opened upon the application of heat to the gate;

Figure 7a shows a cross-section of a pathway having a wax gate which has been closed, and a heating tool;
Figure 7b shows a cross-section of the pathway of Figure 7a, where the pathway has been reopened to the flow of fluid upon application of heat and pressure;
Figure 7c shows a plan view of Figure 7b;

Figure 8a shows a plan view of a wax clamp used in a chamber, in which the clamp may be initially closed or open;
Figure 8b shows a cross-section of an deflated chamber having a wax clamp;
Figure 8c shows a cross-section of an inflated chamber having a wax clamp;

Figure 9a shows a plan view of a chamber containing a gas generating mixture, in fluid connection with a pathway having an initially closed wax gate;
Figure 9b shows a plan view of the chamber of Figure 9a, having an opened wax gate, where fluid has flowed into the chamber (under capillary action or external pressure) and is in contact with the gas producing material contained within the chamber;
Figure 9c shows a plan view of the chamber of Figure 9a where fluid has been driven out of the chamber by a gas; and
Figure 9d shows a cross-section of the chamber and connecting pathway of Figure 9a.

Referring to Figure 1, there is shown a chemical assay device 10 for analysis of blood, or other biological fluid. End products of a reaction or assay may be detected using optical methods. For example, a colour change may be detected by a photo-diode, or a fibre-optic system, or visually. The device has an area typically about 50 cm^2 and is 3 to 10 millimetres thick. The device 10 may be significantly larger or smaller depending on the complexity of the processes to be carried out and the volumes of fluids to be processed. In this particular embodiment, the assay device 10 is configured to carry out an immunological assay and this will be described so as to illustrate a method of operation of the invention.

Assay device 10 comprises a generally square, substantially planar substrate in which a number of chambers 14 are interconnected by pathways. Fluid control in the device 10 is by way of wax gates and clamps, which are shown in Figure 1 in their initial (open or closed) states.

The device 10 includes an inlet port 12 in fluid connection with a reaction (e.g., lysing) chamber 14. Chamber 14 leads to waste depot 16 and filter chamber 18 via separate fluid channels. Filter chamber 18 is in fluid connection with chambers 22 and 24, and with processing chamber 20. Chamber 22 is initially filled with a wash solution, and chamber 24 is filled with an eluent which is used to displace material from processing chamber 20.

Processing chamber 20 is connected to waste depot 16 via a channel 64. Channel 64 leads to an array of metered read-out cells 26, 28, 30 and 32. Air from read-out cells 26 to 32 exits into channel 65. A channel 6 is provided and links channels 64 and 65. The operation of one of the metered readout cells will now be explained with reference to readout cell 26 of Figure 1.

The analysis area of device 10 comprises a large-bore inlet port 25 leading to a fixed-volume cell 26, which in turn is connected to a narrow-bore outlet tube 27. Tube 27 leads to pathway 65, and ultimately to waste depot 16. The structure comprising parts 25, 26 and 27 has a fluid impedance which is dependent on the amount of fluid therein. Fluid can flow freely into the cell until the narrow-bore section is reached, at which stage the force needed to continue driving the fluid into the cell is greatly increased. At this point the fluid, which flows most readily along the path of least resistance, diverts to the conduit leading to the next cell (28 in this case), and so on. Thus each of the cells 26, 28, 30, 32 is filled in turn, and the volume of fluid entering each cell can be controlled.

Chamber 20 is also connected to chamber 38 via a fluid pathway, and chamber 38 leads to chamber 40. Chambers 38 and 40 both contain wax clamps. Both chambers 38 and are initially deflated.

Waste depot 16 connects to breather tube 13, and reservoir 22 leads to breather tube 11. Breather tubes 11 and 13 ensure that fluid moves freely within the device. Also tubes 11 and 13 when connected to non-critical regions ensure that any excess fluid does not interfere with any on-going analysis.

Reservoir 24 is connected to chamber 42. Chamber 42 is pre-filled with a dry mixture which, when in contact with a liquid, produces a gas. This is shown diagrammatically in Figure 9.

Wax gates are situated in fluid pathways in order to control flow of fluid between the chambers. In Figure 1, gates are shown in their initial states. For example, fluid flow is initially obstructed at gate 34, whereas initially fluid is allowed to flow freely through gate 36.

Referring again to Figure 1, a typical sequence of events for an immunological assay is now described. A blood sample (not shown) is injected into the assay device via inlet port 12. Blood fills reaction chamber 14 by capillary action and/or hydrostatic pressure, and excess blood enters the waste depot 16. The blood remains in chamber 14 for as long as is required for cell lysing to occur with a reagent. The reagent is introduced into this chamber in a predetermined dose during the manufacture of the device. Heat is then applied to gates 44, 46 and clamp 48 in order to close gate 44, open gate 46, and release clamp 48 and thereby actuate partial vacuum chamber 38.

The lysed blood is then urged through filter chamber 18 by way of a partial vacuum, and serum fills processing chamber 20. An antigen in the blood serum then bonds to an antibody which has been tagged onto, for example, glass or ceramic beads (not shown). The beads are pre-dosed and introduced in chamber 20 at the manufacturing stage.

The serum is then washed from the glass beads in chamber 20 by activating heaters at gates 50, 52 and 54, and clamp 56. A partial vacuum in chamber 40 draws wash fluid from chamber 22 through chamber 20 leaving the antigen bound to the particles in chamber 20. Waste wash solution and serum enter chambers 38 and 40.

The next step is elution. Activating heaters placed at gates 57, 58, 60, 36, 34 and 62 allows the fluid in the reagent reservoir 24 to wet a gas producing powder. Fluid is then driven by the gas through chamber 20 towards analysis cells 26, 28, 30 and 32. As eluent from reservoir 24 passes through chamber 20, antigen is released from the beads and carried in the eluent to the analysis cells. These cells contain reagents such as enzyme systems which react with the antigen, causing either a colour change in the solution, or a change in fluorescence. Any recognised method of optical analysis can then be used for detection and measurement of end products of the reactions. Once cells 26, 28, 30 and 32 are filled, resistance to fluid flow increases in the narrow exit channels 27, 29, 31, and 33. Excess fluid is then expelled to waste depot 16 through channel 6.

Finally, activating heaters at gates 66, 68 and 70 seals the fluids within the device for hygienic disposal.

Further embodiments of the invention are described now with reference to Figures 2 to 8 inclusive.

Figure 2 shows a plan view of a section of a pathway having a wax gate 73 that closes the pathway to the flow of fluid on application of heat. A volume of wax is contained in recess 72. Pathway 75 has a region of hydrophobicity 76 in order to guide the flow of wax. Upon application of heat to gate 73, the wax melts and flows into the fluid pathway to obstruct the flow of fluid therein. Air enters through inlet 74 and replaces the wax in recess 72. Thus air prevents flowback of the molten wax. As the wax cools fluid flow along the pathway becomes obstructed.

In Figure 3 a plan view of a section of pathway having a wax gate 77 is shown. Gate 77 closes pathway 75 to the flow of fluid on application of heat to the gate. A volume of wax 78 is situated in the path of the fluid, only partially obstructing the fluid flow. Upon application of heat to the gate, the wax melts and flows to block the pathway guided by the area of hydrophobicity 76. As the wax cools fluid flow along the pathway becomes obstructed.

Figure 4 shows another form of heat closable pathway. A volume of wax 78 is situated in pathway 75, only partially obstructing the flow of fluid. In order to block the channel, a moveable heat sealing tool 80 is used to apply both pressure and heat, completely sealing the channel. This form of gate requires that at least one sheet forming the pathway is formed from deformable material. If the deformable material can be directly sealed to the second sheet (by heat, pressure or otherwise), then wax is not required.

Figures 5, 6 and 7 all represent forms of heat openable pathways, that is, wax gates that are initially closed to fluid flow in the pathway.

Figure 5 shows a plan view of a section of a pathway 75 having a gate 79 that opens the pathway to the flow of fluid on application of heat to the gate. A volume of wax is situated in the pathway between two recesses 72. The recess has a region of hydrophobicity 76 in order to guide the flow of wax. Upon application of heat to the gate, the wax melts and

flows into the recess. Air exhausts via inlet 74 and is replaced by the wax in the recess, preventing flowback of the molten wax. As the wax cools the fluid pathway opens.

Referring to Figure 6, there is shown a plan view of a section of pathway 75 having another form of wax gate 81. The gate opens the pathway to the flow of fluid on application of heat to the gate. A volume of wax 78 is situated in the path of the fluid, and seals the pathway, preventing fluid flow. Upon application of heat to this wax gate, the wax melts and flows in the pathway guided by the area of hydrophobicity 76. As the wax cools, the fluid pathway remains open.

Figure 7 shows another heat openable gate situated in pathway 75. A volume of wax 78 is situated in the pathway, obstructing the flow of fluid. In order to open the pathway to allow the flow of fluid, a moveable heat sealing tool 80 is used to apply both pressure and heat to the pathway. The shape of this heat sealable tool allows the wax to be deformed, forming a channel in the wax. This type of gate requires that at least one sheet forming the pathway is deformable and resilient, so that the sheet may return to its original state and leaves the pathway open.

In addition to the aforementioned wax valves, components to actuate fluid flow may be required. Capillary action may be used to provide some fluid movement, and this can be extended by opening further fillable or absorbent areas or by opening valves of the types previously described. However, greater flexibility is achieved by employing structures capable of generating pressure differentials, and these are shown in Figures 8 and 9.

Figure 8 shows a chamber 38 containing a wax clamp 78. Changing the shape and volume of chamber 38 provides a pressure differential to drive (or suck) fluid flow in the connected pathways and chambers. Two sheets of synthetic plastics material 37a and 37b are fixed together using a volume of wax 78 in order to produce a deflated chamber 38. Upon application of heat, wax clamp 78 melts. This allows the surfaces of chamber 38 to separate thereby inflating the chamber. This results in a pressure change, and fluid is sucked through interconnecting pathways. Chamber 38 may be returned to its deflated state by the application of an external pressure (shown in the direction of arrow A) and by heating the wax. As the wax cools, the deformable surfaces are fixed together.

Figure 9 shows a further means of generating pressure in order to drive the flow of fluid. Figure 9 shows a chamber 88 connected to a pathway having a closed wax gate 86. The chamber contains a dry gas generating mixture 82, for example sodium bicarbonate with tartaric acid. On applying heat to the wax gate 86, the wax flows to unblock the pathway 85. A solution 84 flows into the chamber 88, wetting the gas generating mixture and causing the generation of a gas. The gas increases the pressure inside the chamber, ejecting the liquid that has flowed into the chamber and propelling it along one or more interconnecting pathways. In addition to the gas generating mixture, an inert absorbent material may be included in the chamber, or the chamber may be filled with capillary matting which acts as a wick.

The invention has been described by way of a number of embodiments, and it will be appreciated that variation may be made to these embodiments without departing from the scope of the invention.

Claims

1. An assay device having at least one chamber in fluid connection with at least one pathway, the pathway being adapted to allow fluid to flow to/from said chamber, characterised in that there is provided a volume of deformable material in the pathway, whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

2. An assay device having at least one chamber in fluid connection with at least one pathway, the pathway being adapted to allow fluid to flow to/from said chamber, characterised in that there is provided a volume of deformable material situated in a recess, the recess located substantially adjacent the pathway, whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

3. A device according to claim 1 wherein there is at least one recess located substantially adjacent the pathway.

4. A device according to claim 2 or claim 3 wherein an opening is provided, the opening acts as a vent to or from the recess.

5. A device according to claim 1 wherein the deformable material is situated in the pathway such that the pathway is partially obstructed.

6. A device according to either claim 1 or claim 3 wherein a volume of the deformable material is situated in the pathway such that the pathway is substantially obstructed.

7. A device according to any preceding claim wherein the chamber comprises a deformable envelope and at least two points of the envelope are connected by way of a volume of deformable material.

8. A device according to any preceding claim wherein a region of the device has at least one hydrophobic portion so that the flow of the deformable material is guided along a predetermined path.

9. A device according to any preceding claim wherein the deformable material is thermally deformable.

10. A device according to any of claims 1 to 8 wherein the deformable material is mechanically deformable.

11. A device according to any preceding claim wherein heating means is provided.

12. A device according to any preceding claim wherein a means for removing heat is provided.

13. A device according to any preceding claim wherein the at least one surface defined by or in the device is resiliently deformable.

14. A device according to any preceding claim wherein a plurality of volumes of deformable material are provided, each volume being accessible independently one from another.

15. A device according to any preceding claim having at least one component from the set of: an inlet port, a reaction chamber, a waste depot, a filter chamber, an infinity capture and processing chamber, a wash solution/reagent reservoir, an array of metered readout cells, and a breather tube.

16. A device according to any preceding claim, in which heat is selectively applied to one or more of the volumes of the deformable material.

17. A device according to any preceding claim, in which heat is selectively removed from one or more volumes of the deformable material.

18. A device according to any preceding claim, in which pressure is selectively applied to at least one region contained within the device.

19. A device substantially as described with reference to the Figures.

20. A method of performing chemical analysis substantially as described with reference to the Figures.

21. A method of manufacturing an assay device, including the steps of: a) defining at least one fluid pathway on a substrate; b) defining at least one reaction chamber on a substrate; c) forming at least one component composed of a heat deformable material in the device; and d) bonding together at least two substrates to form the device.

22. A method of manufacturing the device according to claim 22 , wherein the at least one fluid pathway may be formed by: a) printing, b) etching, c) ablation, d) use of a mould, e) cutting, or a combination of any of steps a) to e).

23. A method of manufacturing the device according to claim 22, wherein the at least one reaction chamber may be formed by: a) printing, b) etching, c) ablation, d) use of a mould, e) cutting, or a combination of any of steps a) to e).

24. A method of manufacturing the device according to claim 22, wherein the at least one component composed of a heat deformable material may be formed by: a) printing of a deformable material onto the substrate, b) etching, c) pick-and-placing of components, d) injection of molten material into device using feeder tubes, or a combination of steps a) to d).

25. A method of manufacturing the device according to claim 22, wherein the at least one substrate may be bonded by: a) adhesives, b) curing, c) mechanical fixing, d) heating, e) anodic bonding, or a combination of steps a) to e).

ABSTRACT

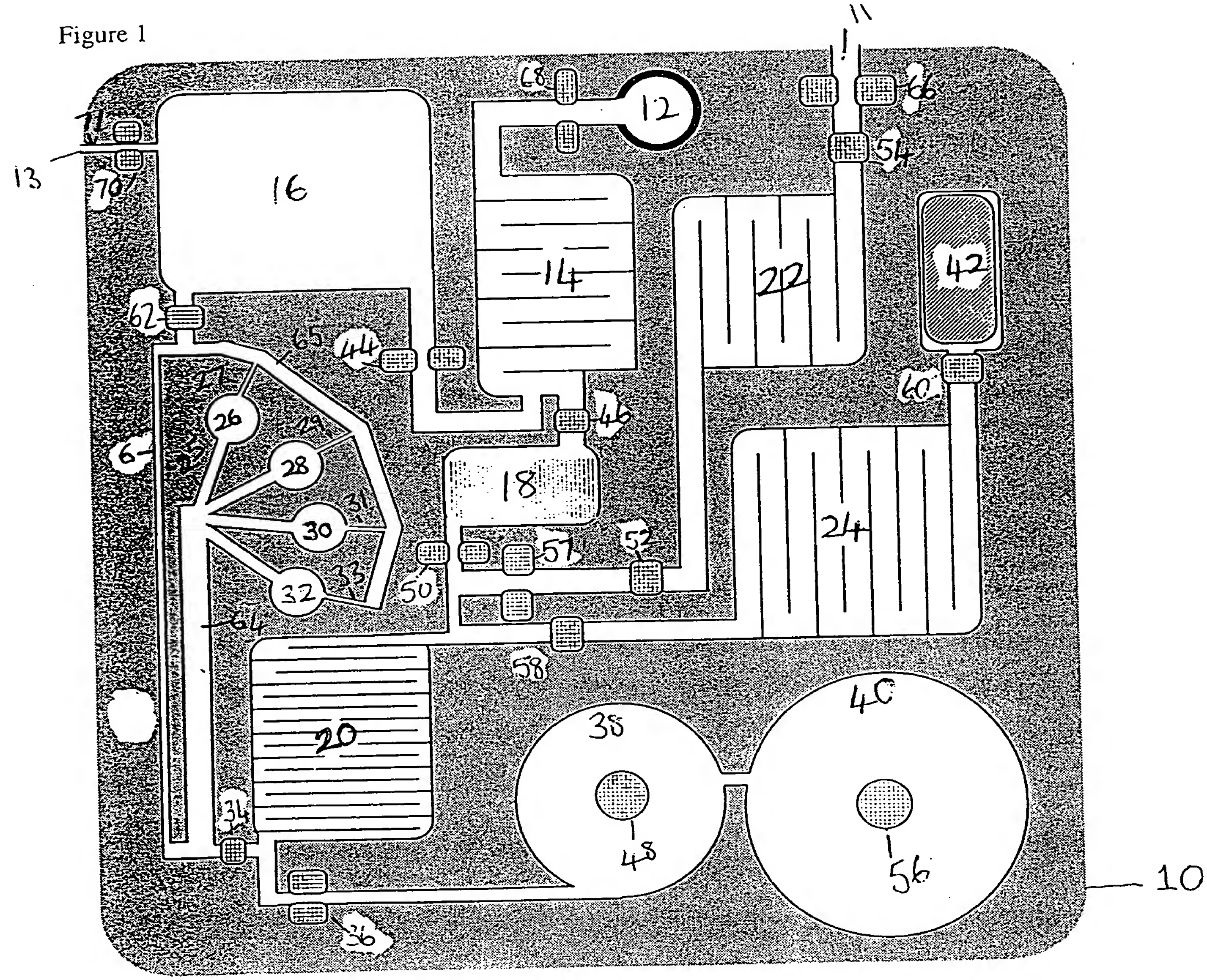
An apparatus for controlling the rate of flow of a fluid in a pathway by the use of wax valves and clamps, which change their size, position, state or function on application of heat and/or pressure.

A disposable chemical assay device, and a method of using the device incorporating the apparatus are described. The assay device 10 includes an inlet port 12, a reaction chamber 14, a waste depot 16, a filter chamber 18, a processing chamber 20, wash solution/reagent reservoirs 22 and 24, an array of metered readout cells 26, 28, 30 and 32, and breather tubes 11 and 13;

The invention, in a preferred embodiment, offers the advantage over existing assay devices because the condition or state of wax valves and clamps may be changed. Therefore more complex operations and procedures may be performed by the assay device than has been previously achievable.

Figure 1 accompanies the abstract

Figure 1



NOT TO BE AMENDED

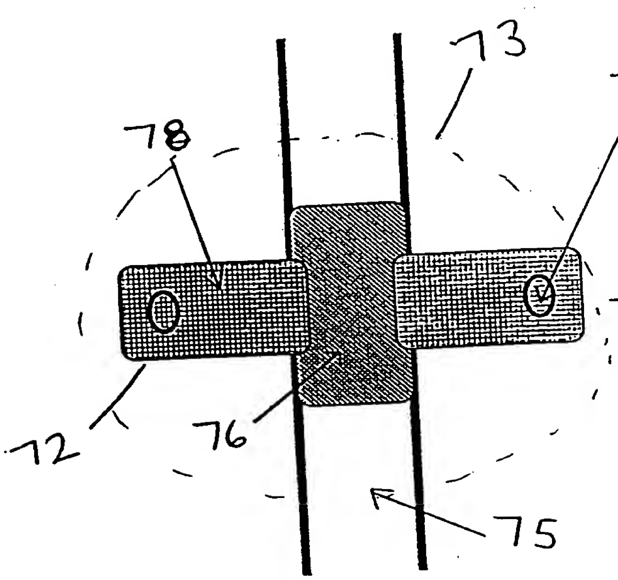


Figure 2a

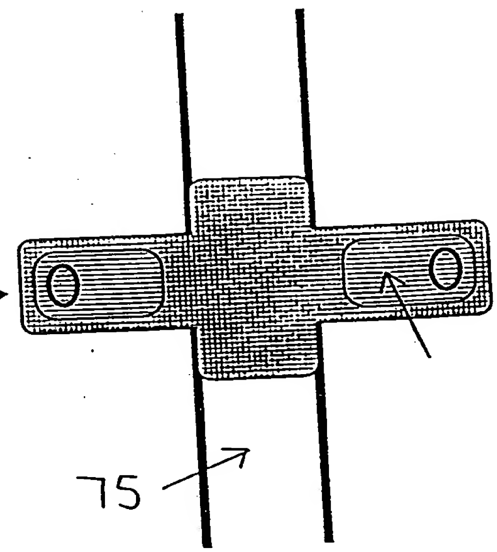


Figure 2b

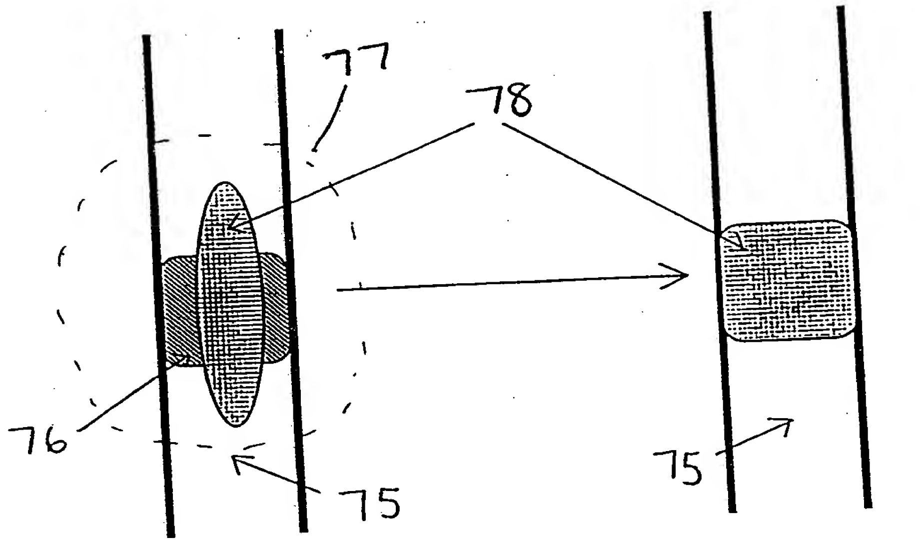


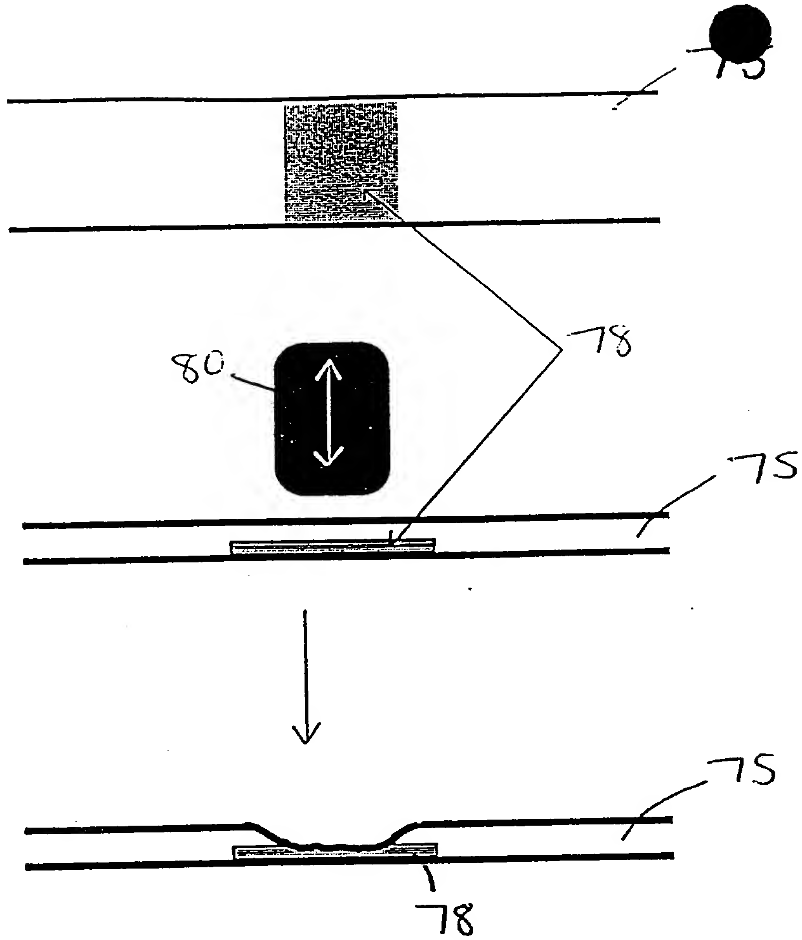
Figure 3a

Figure 3b

Figure 4a

Figure 4b

Figure 4c



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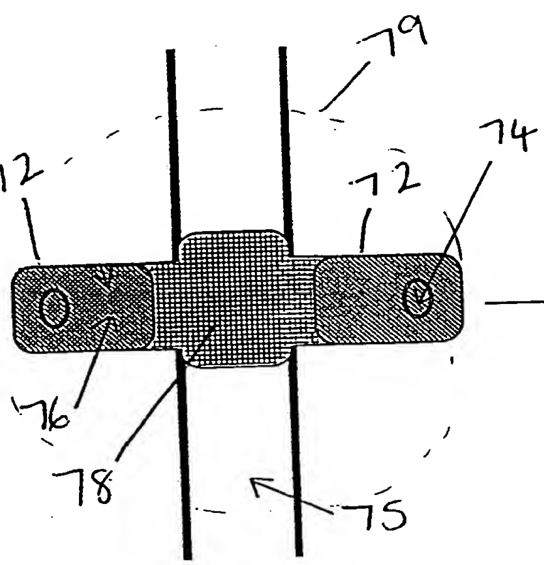


Figure 5a

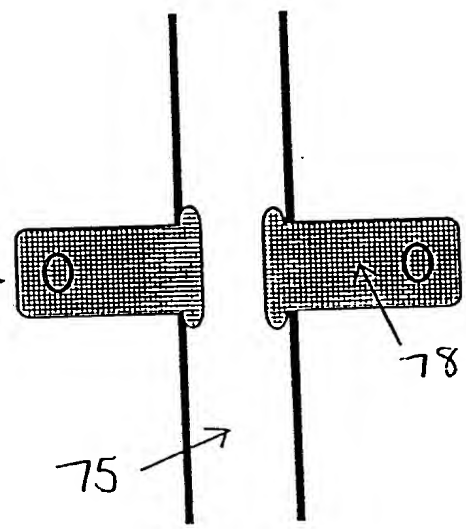


Figure 5b

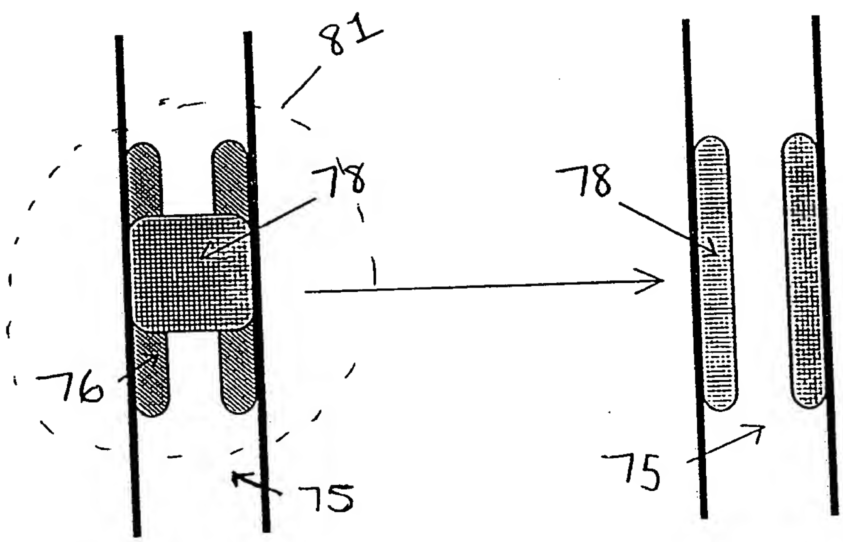


Figure 6a

Figure 6b

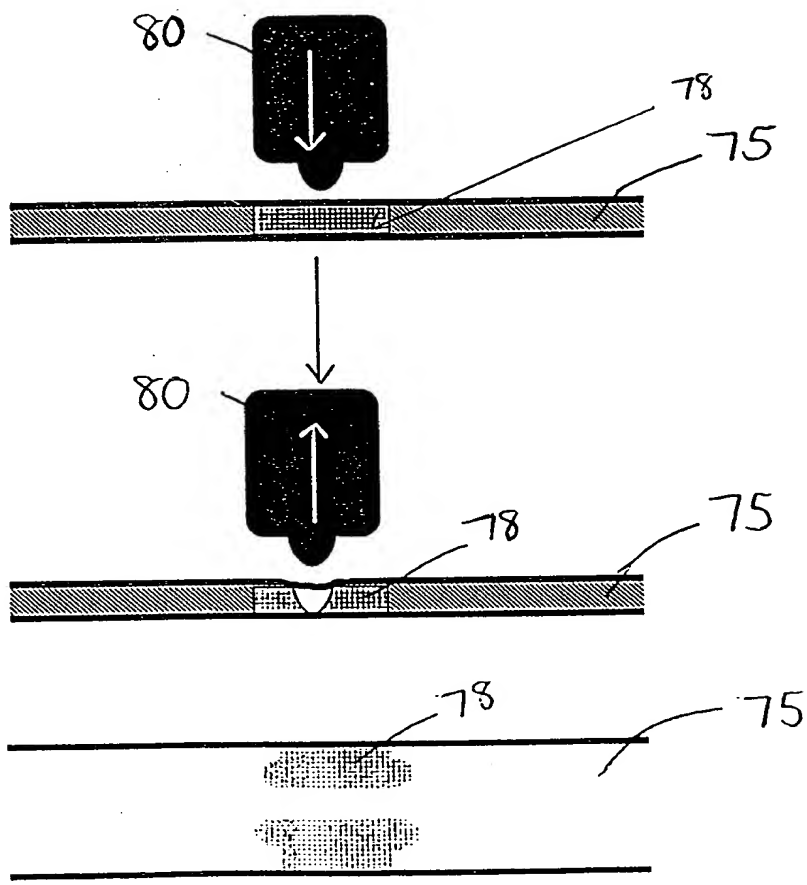


Figure 7a

Figure 7b

Figure 7c

Figure 8a

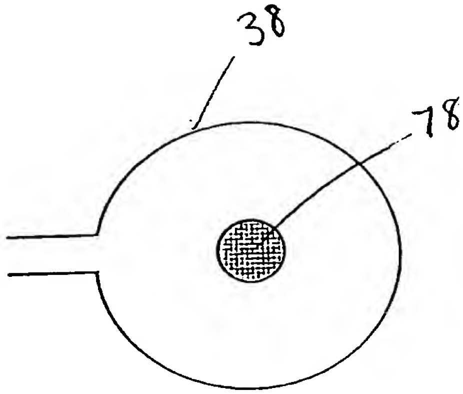


Figure 8b

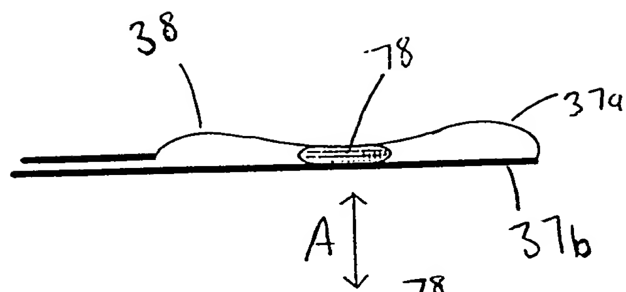


Figure 8c

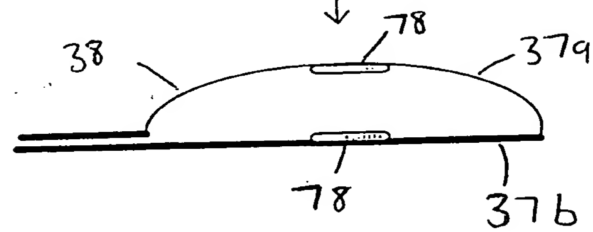


Figure 9a

Figure 9d

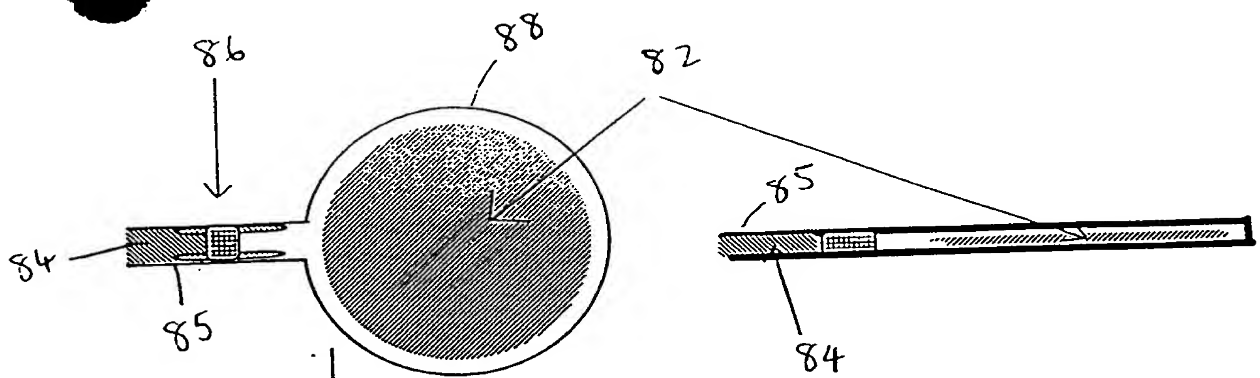


Figure 9b

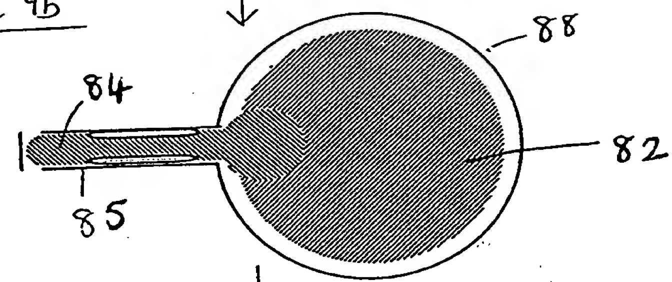
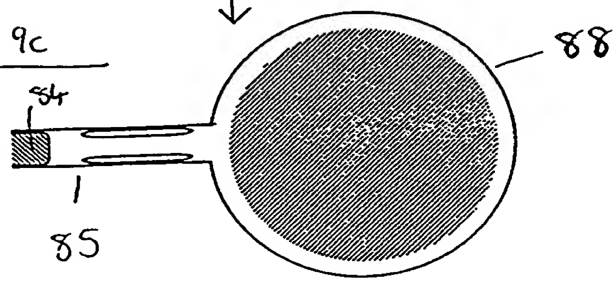


Figure 9c



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